
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Mulligan *et al.*

Serial No.: 08/252,710 Group Art Unit: 1805

Filed: June 2, 1994 Examiner: G. Elliott

For: RETROVIRAL VECTORS USEFUL FOR GENE THERAPY Attorney Docket No.: 8141-113

DECLARATION UNDER 37 C.F.R §1.132

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, Lawrence Cohen, declare and state that:

1. I am an employed by Somatix Therapy Corporation as Vice President of Research. I have worked at Somatix Therapy Corporation since 1988. My Curriculum Vitae is presented herewith as Exhibit 1.

2. I am familiar with the Specification and Claims of the above-identified patent application (heretofore the "present application") and the Office Action mailed April 17, 1996 (Paper No. 12).

3. It is my understanding that the Examiner contends that the Claims of above-identified application are obvious over the teaching of Cone and Mulligan, 1984

my opinion that one of ordinary skill could not have used the teaching of Cone to practice the presently claimed invention.

6. It is also my opinion that, prior to the present invention, the cell lines and vectors taught by Cone would have not provided one of ordinary skill with a general expectation that mammalian cells could be successfully transduced without the use of selectable markers. In fact, the first published disclosure of human primary tumor cells transduced without selection (i.e., Jaffee *et al.*) was made nine years after Cone was published. During those nine years, novel retroviral packaging cell lines were constructed (as described in U.S. Patent No. 5,449,614 "'614", issued September 12, 1995), and the equally novel retroviral vectors of the present application were constructed. Jaffee *et al.* obtained these pioneering results after combining novel vectors and a packaging cell line that were both developed well after Cone was published. It should also be noted that one of the incentives for producing the claimed vectors and the packaging cells described in the '614 patent was the realization that many methods of *ex vivo* or *in vivo* gene therapy would not be compatible with the prolonged periods of selective culture used in previous methods of transduction (including the methods specifically described by Cone). In many respects, the above insight played a key role in motivating the development of retroviral vectors that lack a selectable

(Proc. Natl. Acad. Sci. *81*:6349-6353) in combination with other references.

4. I have read and am familiar with the above-identified reference by Cone and Mulligan ("Cone").

5. It is my opinion that, given the teaching in the Cone reference, one of ordinary skill in the art as of the filing date of the present application would not have had a reasonable expectation of successfully practicing the claims of the present application. My opinion is based on the fact that subsequent studies have shown that retroviral titers of the concentration disclosed by Cone (">$10^5$") are insufficient to effectively transduce mammalian cells without selection. For example, to my knowledge the first published report that primary human tumor cells could be transduced without selection was made in 1993 by Jaffee *et al.*, 1993, Cancer Research *53*:2221-2226 ("Jaffee", attached as Exhibit 2). Jaffee used a novel retroviral vector that is an embodiment of the vectors described in the above-identified application. To my knowledge, retroviral transduction without selection (as reported in Figure 1 of Exhibit 2) generally requires high titer stocks of transducing virus. In particular, a <u>minimum</u> titer of approximately <u>5 x $10^6$</u> transducing virus per ml is required. This concentration of retrovirus is at least several fold higher (if not a full order of magnitude higher) than the retroviral titers reported by Cone. Accordingly, it is

marker (i.e., the presently claimed vectors). Cone neither taught nor suggested the above insight.

7. I hereby further declare, under penalty of perjury under the laws of the United States of America, that all statements made herein of my own knowledge are true and that all statements made upon information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 10/11/96

By: _____
Lawrence Cohen, Ph.D.

# Exhibit 1

**Curriculum Vitae**
**LAWRENCE K. COHEN, Ph.D.**

**PERSONAL:**

Address: 5670 Cabot Drive
Oakland, California 94611

Born: April 19, 1953

**EDUCATION**

1974 B.A., Grinnell College
Grinnell, Iowa

1976 M.S., University of Illinois
Urbana, Illinois

1981 Ph.D., University of Illinois
Urbana, Illinois

**POSTDOCTORAL TRAINING:**

1981-1983 **RESEARCH FELLOW IN MICROBIOLOGY AND MOLECULAR GENETICS,**
Dana Farber Cancer Institute,
Harvard Medical School, with Jack L. Strominger

1983-1985 **RESEARCH FELLOW IN BIOLOGICAL CHEMISTRY,**
Harvard Medical School, with Bryan E. Roberts

**AWARDS:**

1981 American Cancer Society Fellowship

1982-1985 NIH, National Research Service Award

1985-1986 Medical Research Foundation Grant

**PROFESSIONAL EXPERIENCE:**

1993-present **VICE PRESIDENT, RESEARCH AND DEVELOPMENT**
Somatix Therapy Corporation
Alameda, California

1992-1993 **DIRECTOR, MOLECULAR BIOLOGY**
Somatix Therapy Corporation
Alameda, California

1991-1992 **MANAGER, MOLECULAR BIOLOGY**
Somatix Therapy Corporation
Alameda, California

1988-1991 **PROGRAM LEADER**
**VASCULAR GRAFT PROGRAM**
Somatix Corporation
Cambridge, Massachusetts

1987-1988 **SENIOR SCIENTIST AND GROUP LEADER**
**OF VIROLOGY & TISSUE CULTURE**
Applied bioTechnology, Inc.
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1986-1987 **RESEARCH SCIENTIST**
Applied bioTechnology, Inc.
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1985-1986 **LECTURER IN BIOLOGICAL CHEMISTRY**
Harvard Medical School
Cambridge, Massachusetts

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2. Lynn, S.P., Cohen, L.K., Gardner, J.F. and S. Kaplan. Characterization of a site specific restriction endonuclease from Rhodopseudomonas sphaeroides. J. Bacteriol. 1979; **138:**505-509.

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4. Cohen, L.K. and S. Kaplan. The non-detergent solubilization and isolation of intracytoplasmic membrane polypeptides from Rhodopseudomonas sphaeroides. J. Biol. Chem. 1981;**256:**5901-5908.

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L.K. Cohen, B. Guild, L.F. Rayfield, P. Robbins and R.C. Mulligan. Retroviral vectors useful for gene therapy. U.S. Patent Application #07-786015, Filed 10/31/91